187 Preclinical and early osteoarthritis

Virginia Byers Kraus

Key Points

- Preclinical osteoarthritis (OA) can be considered the earliest disease phenotype characterized by serologic abnormalities before abnormalities detected by sensitive imaging modalities such as ultrasonography or magnetic resonance imaging.
- The strongest evidence for the existence of preclinical OA is provided by the sequence of biomarker changes and pathologic stages observed after a major joint injury; this paradigm provides hope that these observations can be translated into diagnostic algorithms for the early detection of idiopathic OA.
- Early OA might be considered the presence of joint pain in combination with clinical signs such as joint line tenderness and crepitus on physical examination in the setting of little or no OA on a radiograph.
- Conventional OA risk factors function poorly for detection of preclinical and early OA.
- Early diagnosis and intervention in OA would improve the likelihood of disease modification and thereby reduce medical costs, morbidity, and disability.
- Reclassification of the disease as no longer a purely radiographic entity to a disease process that includes preclinical, preradiographic, and radiographic stages would provide a scenario amenable to the development of primary, secondary, and tertiary prevention strategies.

DEFINITION OF PRECLINICAL AND EARLY OSTEOARTHRITIS

Clinical osteoarthritis (OA) has generally been synonymous with the presence of radiographic changes of OA, including joint space narrowing and osteophyte formation. However, there is a need to be able to identify disease earlier because this would represent the best opportunity to understand basic disease mechanisms and intervene before irreversible joint damage and pain set in. There are currently no agreed upon criteria for preclinical OA and early OA. Preclinical OA is the very earliest phase of the disease before it becomes clinically recognizable. Alternatively, it is the phase before the appearance of symptoms (Fig. 187.1). With the advent of more sensitive imaging techniques, preradiographic stages of disease are recognizable—both magnetic resonance imaging (MRI)[1-3] and ultrasonography (US)[4,5]—have provided concrete evidence for joint structural abnormalities predating the quintessential radiographic changes we associate with OA. These imaging techniques establish a new threshold for what constitutes definitive "clinically recognizable" disease.

It is currently difficult to define preclinical OA as the stage that predates symptoms for two reasons. For one, joint symptoms can be ascribed to multiple causes, and thus symptoms outside the context of the clinically recognizable structural changes of OA cannot currently be definitively diagnosed as being attributable to an OA disease process. Moreover, symptoms of OA wax and wane and might appear and disappear during the preclinical phase of OA, just as they do during the clinically recognizable phases of disease (see Chapter 181 for a discussion of symptoms of OA). Until our understanding and diagnosis of the cause of early joint symptoms improve, this potentially waxing and waning symptom threshold abrogates our ability to currently define preclinical OA as a presymptomatic stage. Therefore, herein, preclinical OA is defined as the early phase of disease before OA-related abnormalities are detectable with MRI or US (or other sensitive imaging modality) (see Fig. 187.1). "Preclinical OA" described here should be distinguished from "preclinical models of OA," which refers to animal models of disease[6] that are discussed in Chapter 182.

The term *early OA* is often used to refer to mild or moderately severe radiographic OA. More recently, the term *early OA* has been used to refer to preradiographic or even earlier phases of disease (Fig. 187.2). A panel of OA researchers recently suggested draft classification criteria for early knee OA for use in clinical studies consisting of the presence of joint pain in combination with clinical signs such as joint line tenderness and crepitus on physical examination in the setting of little or no radiographic OA.[7] Viewed more broadly, at least four scenarios might be considered to be consistent with early OA (see Fig. 187.2), including both symptomatic and asymptomatic presentations.

EVIDENCE FOR PRECLINICAL AND EARLY OSTEOARTHRITIS

The World Health Organization defines chronic diseases as ones of long duration and generally slow progression (http://www.who.int/topics/chronic_diseases/en). Chronic diseases are characterized by complex causality, multiple risk factors, long latency periods, a prolonged course of illness, and functional impairment or disability (http://www.aihw.gov.au/chronic-diseases). Many conditions can be considered chronic diseases, including coronary heart disease, chronic obstructive pulmonary disease, and osteoporosis. These chronic diseases are viewed as amenable to preventive measures; such perception has led to the development of public health strategies to encourage healthy environments and lifestyles. For instance, it has led to efforts to control blood pressure and cholesterol to reduce the burden of heart disease and stroke. OA well fits this chronic disease paradigm. Such recognition that OA fits this chronic disease paradigm would be expected to broaden the scope of study beyond a focus on diagnosis, monitoring, and treatment of end-stage radiographic disease to include efforts to identify and characterize the preclinical and preradiographic stages to spearhead more effective efforts to reduce the burden of disease. Moreover, the process of disease involves the interaction of cartilage with all other structural elements of the joint and mechanical factors; it is reasonable to assume that a similar holistic process is operational in preclinical and early OA.

The strongest evidence for the existence of preclinical OA is provided by the sequence of pathologic stages observed after a major joint injury. Unlike primary idiopathic OA, posttraumatic OA has a known time of onset, making it much more tractable as a method of detecting and monitoring preclinical OA. Based on longitudinal studies, intraarticular pathogenic processes, initiated at the time of injury, result in radiographic OA 10 to 20 years later[8] and preradiographic OA based on MRI much sooner.[9,10] Longitudinal studies of the aftermath of severe joint injury have convincingly established the existence of a prolonged preclinical molecular phase of disease characterized by protein and microRNA biomarker abnormalities.[11-20] After knee injury, cartilage degradation is favored over repair, with increased collagen cleavage.[21-23] Within the first month after joint injury in humans, elevations have been documented in synovial fluid concentrations of cartilage proteoglycan fragments,[11,23] metalloproteinases (MMP-3/stromelysin-1),[13,16] tenascin-C,[19] and collagen fragments.[23,24] Aggrecanase cleavage of aggrecan (at 392Glu-393Ala in the interglobular domain) is one of the early key events in arthritis and joint injuries.[17,18,25] Elevations of cartilage components in the serum can persist over decades after joint injury.[12-16] The sustained increased release of cartilage macromolecular fragments after joint trauma is thought to be a harbinger for the development of posttraumatic radiographic OA in patients with injuries. Many of these fragments are not only biomarkers of early disease pathology but themselves also act as disease-associated molecular proteins (DAMPs) as part of an innate immune response[26] to induce and prolong inflammation after joint injury[19,27] and therefore represent biomarkers within the causal pathway of disease. Consistent with this paradigm, joint inflammation by MRI predicts incident radiographic knee OA, even in the absence of knee pain.[28]

In the course of idiopathic (primary) OA, devoid of a clear inciting severe acute injury, it is difficult to track early events. Nevertheless, a few studies have identified premonitory biomarker alterations that herald the later appearance of idiopathic radiographic OA. In the Chingford cohort, with serial samples and knee radiographs available over the course of 23 years, two serum biomarkers, cartilage oligomeric matrix protein (higher) and aggrecan (lower), predicted in advance, by as much as 10 years, incident radiographic knee OA.[29] In another study, serum cartilage oligomeric matrix protein (COMP) and hyaluronan (HA), predicted the occurrence, 7 years later, of incident knee joint space narrowing (COMP and HA) and osteophyte

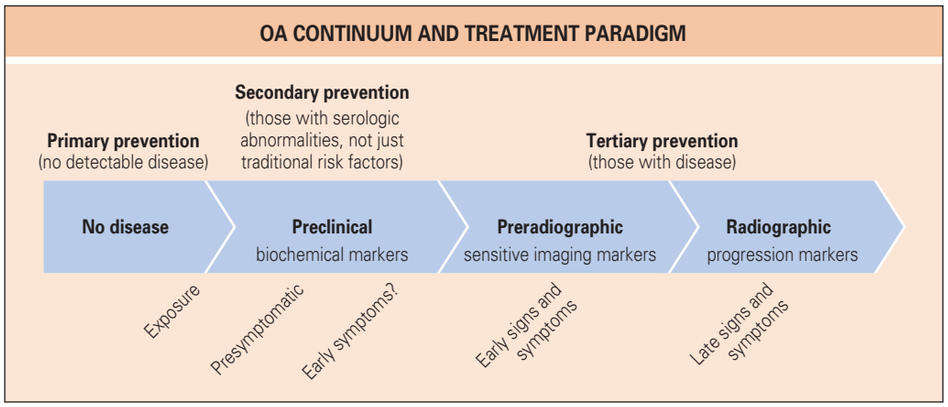

FIG. 187.1 In this schema, osteoarthritis (OA) progresses through stages. Although tools for identifying preclinical OA are limited, events ensuing from acute joint injury attest to the existence of a relatively prolonged asymptomatic preclinical phase of OA before preradiographic and later, radiographic stages. Each of these phases demands a different intervention strategy: The earliest preclinical phase with no apparent illness calls for primary preventive interventions to protect the health of the joint and prevent the appearance of clinically recognizable stages of disease; the preradiographic phase of clinically recognizable but early disease requires secondary preventive measures to halt or slow the progress of disease, if possible, in its earliest stages; and the radiographic phase of OA calls for tertiary preventive measures to prevent or reduce the illness of OA, namely the symptoms and disability in the face of a long-term health problem (for a description of illness vs disease, see Kraus and colleagues[64]).

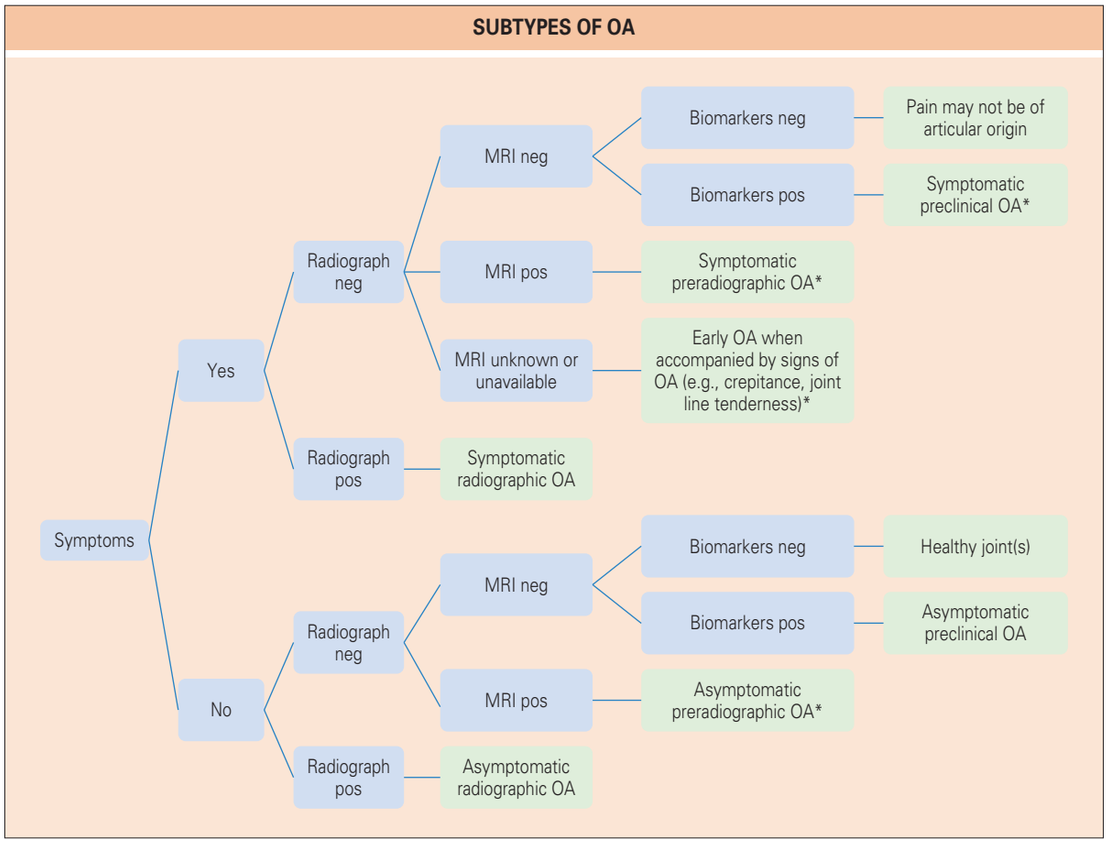

FIG.187.2 In this schema, patients are categorized sequentially on the basis of symptoms, radiography, more sensitive imaging, and biomarkers. Thus, preclinical osteoarthritis (OA), that represented by biomarker abnormalities in the absence of imaging abnormalities, might exist in both symptomatic and asymptomatic patients. Draft classification of early OA has suggested a definition of a symptomatic patient subtype with a negative radiograph but with evidence for signs of OA (e.g., crepitus and joint line tenderness) on physical examination. In addition to this scenario of symptomatic early OA, there are three other theoretically possible presentations of preradiographic early OA (depicted by the *asterisks*). *Neg,* Negative; *pos,* positive.

(COMP).[30] Several studies suggest that serum COMP predicts development of radiographic hip OA between 6 and 8 years later.[31,32] COMP is also increased in the absence of signs of radiographic hip OA in patients with symptoms of hip abnormality.[33] Incident radiographic OA of the hand or knee were predicted 10 years in advance by serum concentrations of four proteins (MMP-7 increased, interleukin-15 increased, plasminogen activator inhibitor-1 increased, and soluble vascular adhesion protein-1 decreased) compared with control participants without radiographic OA in the ensuing decade.[34] These biomarker abnormalities years before idiopathic radiographic OA support the existence of a preclinical phase of OA characterized by serologic abnormalities reflecting preclinical molecular alterations. However, in draft classification criteria for early OA of the knee by the International Early Knee OA (IEKO) working group,[35] biomarkers were not yet included in the criteria because no individual or set of biomarkers was perceived currently to be robust enough for this purpose. The existence of preclinical OA is also suggested by the finding of macroscopically degenerated cartilage from cadaveric donors without a clinical history of OA.[36] Taken together, these studies demonstrate that metabolic alterations in the articular cartilage occur long before radiologic changes are observed and support the chronic disease paradigm of OA that includes a preclinical phase as depicted in Fig. 187.1.

DETECTION OF PRECLINICAL AND EARLY OSTEOARTHRITIS

Although the real-time diagnosis of preclinical OA can be based on biomarkers, these first need to be validated through longitudinal follow-up to confirm their ability to predict preradiographic and radiographic OA. Even more important, the validation of criteria for preclinical OA could be based on the ability to predict decline in how a joint will feel, function, or "survive" (i.e., need for joint replacement).

About half the people with knee pain have no radiographic OA.[3] This poses a challenge for how individuals with joint symptoms attributable to preclinical OA might be discerned from those with joint symptoms from some other cause. Attempts to identify preclinical OA using baseline conventional risk factors signs and symptoms of OA (e.g., age, sex, body mass index, previous injury, pain in the entire leg, difficulty descending stairs, palpable effusion, fixed flexion deformity, restricted knee flexion range of motion, crepitus, morning stiffness, knee bony enlargement) is limited for predicting subsequent incident radiographic OA 3 to 12 years later.[37,38] The limited prognostic ability of conventional risk factors likely occurs in part because the progression from risk factor exposure to development of radiographic OA depends on the variable likelihood that individuals exposed to the same risk factors will progress through the stages of preclinical OA to preradiographic OA to radiographic OA. Work is ongoing to validate early OA criteria (combination of symptoms and signs in the context of a negative radiograph) by determining their positive predictive value for incident radiographic OA. Although OA is highly heritable (~50%), the genetic polymorphisms identified to date only account for about 11% of the heritability.[39] In contrast to monogenic diseases, the risk of OA related to any single gene is low. This accounts for the fact that genetic testing is currently of no clinical value for early detection of disease.

PROGRESSION OF OSTEOARTHRITIS

Because not all radiographic OA progresses to a severe grade of disease or results in joint replacement, by inference, likely not all preclinical or preradiographic OA progresses to early OA and more advanced stages of disease (Fig. 187.3). Several hypotheses are encompassed in this graphic depicting OA as a continuum (preclinical to preradiographic to radiographic). First, the rate of OA progression accelerates with increasing severity of disease. Second, degradation and repair occur simultaneously at all stages of disease (small turning wheels reflecting turnover rates); the greater the degradation rate, the greater the synthetic repair required to meet the demands of the catabolic events (ever larger turnover cycles as the individual progresses further along the trajectory to OA). Third, an excess of catabolism over anabolism drives the trajectory to radiographic OA. Fourth, the mechanisms and rates of progression are probably not uniform among all OA phenotypes.[40] Fifth, the proportion of at-risk individuals that proceed along the OA trajectory at any point in this continuum is uncertain.

Surprisingly little is known about the actual rates of progression through each stage. The rate of progression from preclinical OA to preradiographic OA is entirely unknown. In the specialized circumstance of severe acute joint injury, on average, 50% of individuals develop radiographic OA after 10 to 20 years[8]; this equates to an estimated rate of progression during the preclinical stages of at least 2.5% to 5% annually. As described earlier, the rate of progression from a preradiographic phase to incident radiographic OA may be estimated from one study to be 6.5% to 7.5% annually in the absence or presence of symptoms.[37] The rate of progression from preradiographic to radiographic OA is estimated to be 2% to 19% annually based on calculations using the data from the placebo arms of a number of studies summarized by Manno et al[41] and shown in Table 187.1; higher rates of progression were observed for subsets of subjects with a high symptom load. Because endogenous cartilage repair ability appears to vary significantly by joint type (repair of ankle > knee > hip),[42-44] it is probable that rates of progression from preclinical OA to preradiographic and radiographic OA also vary by joint type as suggested for rates of progression of radiographic OA.[41] One of the most generalizable genetic mutations associated with susceptibility to OA decreases expression of growth differentiation factor 5 (GDF5)[45] (also known as *cartilage-derived morphogenetic protein 1,* CDMP1, a secreted ligand of the transforming growth factor-β superfamily of proteins), which promotes the development, maintenance, and repair of synovial joint tissues, particularly bone and cartilage.[45] It is therefore probable that progression from preclinical to clinically manifest OA is also influenced by genetic factors. Further longitudinal studies are needed to provide more precise estimates of progression for each stage of disease and to understand how these rates may differ by patient subsets, joint type, and risk factors. A better understanding of these differences could enhance our ability to identify at-risk joints early in the disease development stage and avoid the risk of overtreatment in future. The paradigm of joint injury in humans would seem to be the best place to start to gain such information.

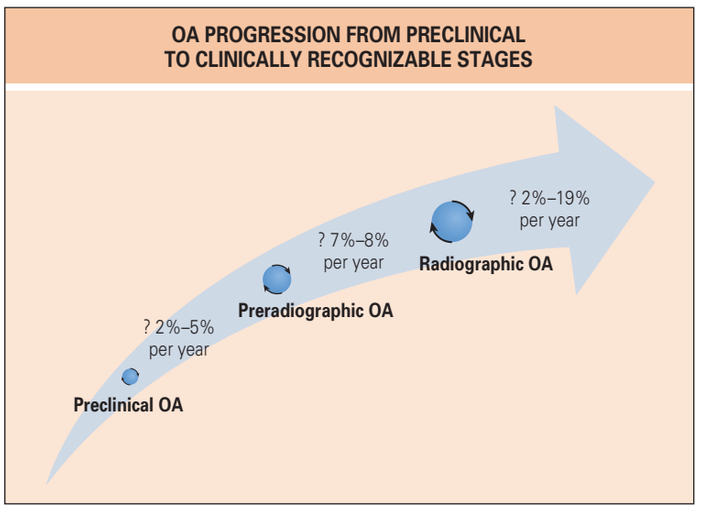

FIG.187.3 At present, the rates of evolution from preclinical to preradiographic to radiographic osteoarthritis (OA)are not precisely known. After a severe acute knee injury, the annual rate of progression in the preclinical phase of OA is at least 2% to 5% annually to account for the overall average risk of developing radiographic OA of 50% by 10 to 20 years later[8]; under less extreme circumstances, the rate is likely lower. Knowledge of rates of progression to radiographic OA from preradiographic OA are limited but may be estimated at 7% to 8% annually given the current information available.[37] The rate of progression of radiographic OA to more severe radiographic stages is estimated to be 2% to 19% annually based on calculations using the data from the placebo arms of a number of studies (summarized by Manno et al[41] and Emrani and colleagues[65]). These should be treated as rough estimates in need of refinement through future longitudinal studies with more comprehensive patient phenotyping of different joints and patient subtypes with sensitive imaging and biochemical markers.

Table 187.1

Summary of studies providing estimates of radiographic osteoarthritis (OA) progression*

Study (*n* in placebo arm)	Study duration (wk/yr)	Participants with radiographic progression among those with baseline symptoms Progressors (*n*)/Total (*n*) (% progression and % per year)	Participants with radiographic progression among all subjects with OA Progressors (*n*)/Total (*n*) (% progression and % per year)
Hip studies			
ECHODIAH (136)	156/3	30/52 (58%; 19%)	30/136 (22%; 7%)
ERADIAS (127)	156/3	24/46 (52%; 17%)	24/127 (19%; 6%)
Knee studies			
PAVELKA (54)	156/3	3/14 (21%; 7%)	3/54 (6%; 2%)
REGINSTER (69)	156/3	12/26 (46%; 15%)	12/69 (17%; 6%)
DOXY (120)	120/2.31	16/37 (43%; 19%)	16/120 (13%; 6%)
GAIT (50)	104/2	4/30 (13%; 7%)	4/50 (8%; 4%)
KOSTAR (625)	104/2	55/316 (17%; 9%)	55/625 (9%; 4%)
STOPP (163)	104/2	19/68 (28%; 14%)	19/163 (12%; 6%)

**Progression defined as change JSW >0.5 mm by study end.*
Data derived from Manno RL, Bingham CO 3rd, Paternotte S, et al. OARSI-OMERACT initiative: defining thresholds for symptomatic severity and structural changes in disease modifying osteoarthritis drug (DMOAD) clinical trials. Osteoarthritis Cartilage 2012;20:93-101.

ECHODIAH, *Evaluation of the Chondromodulating Effect of Diacerein in OA of the Hip;* ERADIAS, *Evaluation of the structure-modifying effect of Avocado-Soybean Unsaponifiables (ASU) in Hip OA;* PAVELKA, *first author of cited publication;* REGINSTER, *first author of cited publication;* DOXY, *Doxycycline trial;* GAIT, *Glucosamine/Chondroitin Arthritis Intervention Trial (of glucosamine and/or chondroitin sulfate);* KOSTAR, *Knee OA Structural ARthritis study (of Resedronate);* STOPP, *The Study on Osteoarthritis Progression Prevention (chondroitins 4 and 6 sulfate).*

TRIGGERING MECHANISMS

As proposed for other diseases,[46] the action of additional potentiating "triggering" mechanisms in the presence of preclinical disease also impacts progression to events, namely progression to preradiographic and radiographic OA. Given the waxing and waning of symptoms, there is every reason to believe that disease progression undergoes nonlinear or phasic progression; this has been supported by the observation that metabolic disturbances in cartilage turnover, reflected by serum COMP concentrations, are phasic and elevated during periods of knee radiographic OA progression.[47] Molecular differences between the cartilage at different joint sites[43,48] and the generation of specific neoepitopes from joint tissue with metabolic disturbances suggest that biomarkers might be developed in the future that reflect disease activity of specific joint types or even of OA specifically. Taken together, biomarkers indicative of joint tissue metabolism could constitute a means of detecting the preclinical molecular stages of OA in advance of preradiographic OA and assess the impact of specific triggering events.

With the recent recognition of a definite and central role for innate immunity in OA,[27] it is now possible to develop a holistic understanding of the pathogenesis of the disease process. From its inception, OA is an active biological disease process, not just a process of mechanical attrition, involving mechanical insults that activate mechanosensors to induce cellular responses to altered mechanical load, including the induction and activation of specific matrix-degrading enzymes[49]; this propagates inflammation through the generation of molecular fragments that act as DAMPs to activate the innate immune response (Fig. 187.4)—a major biologic transducer of disease progression. The cogwheel graphic in Fig. 187.4, which symbolizes the ability of cogs to start and stop, portrays the penchant for OA to wax and wane. This representation shows the interaction of inciting mechanical insults and environmental factors, the potentiation by risk factors and genetics, and the resulting activation of an innate immune response and impaired wound healing[50] leading to the chronic disease process we know as OA. Given this newly emerged understanding of OA disease pathogenesis, it is intriguing to speculate that a robust innate immune response would be protective for infectious disease, particularly in a preantibiotic era but deleterious for potentiating age-related chronic diseases in our current postantibiotic era characterized by increasing longevity. There are in fact hints that the latter is true based on studies showing that low innate production of cytokines upon ex vivo stimulation of blood with lipopolysaccharide is associated with a lower risk of OA and the absence of OA in old age.[51,52] Conversely, a robust repair response would be expected to protect from OA and prevent OA progression along the stages of disease (see Fig. 187.4).

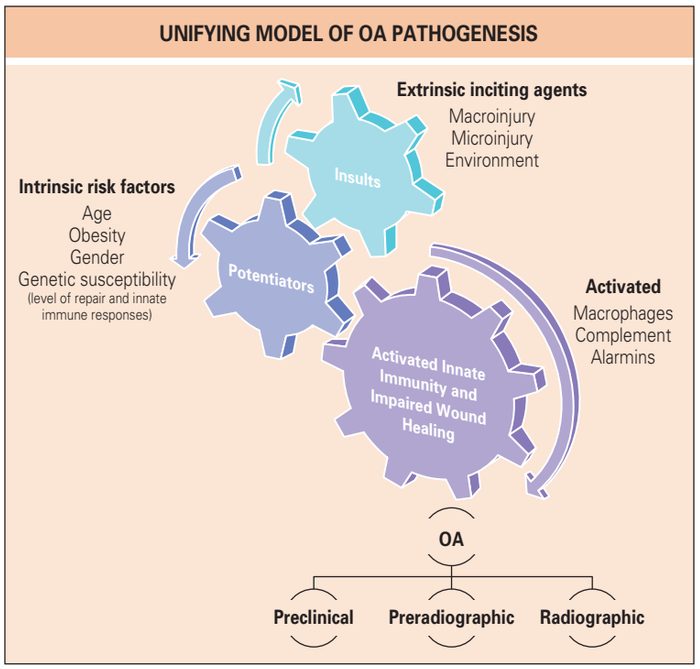

FIG.187.4 This model depicts osteoarthritis (OA) as a condition incited by mechanical insults of microinjury, macroinjury, and environmental factors. The interaction of extrinsic inciting insults with potentiating intrinsic factors determines the relative susceptibility to progression of disease mediated by a biologic innate immune inflammatory response analogous to a chronic wound. The resulting pathology is manifest first as a preclinical (not clinically recognizable) entity, with progression in some individuals to preradiographic stages (detected by sensitive imaging modalities) and eventually to radiographic stages. The interacting cogwheels, able to turn intermittently, depict the penchant for OA activity to wax and wane. The exact timing of the onset of the illness of OA that includes symptoms in this continuum of OA pathogenesis is unclear at present.

TREATMENT PARADIGMS

Osteoarthritis is a slow, insidious, and debilitating process that, similar to other prominent chronic diseases, is likely more amenable to remission early in the disease process. Maintenance of cartilage homeostasis would be expected to halt progression of disease. A tipping of the homeostatic balance in favor of anabolism over catabolism would be expected to reverse disease. As noted by Luyten et al,[53] inactivation of inflammation and joint destruction would be sufficient in some patients at a very early disease stage; however, additional therapies targeting tissue restoration through cell proliferation and differentiation might be needed to achieve the ultimate goal of complete recovery of structural joint integrity. The pattern of biomarker alterations observed after joint injury matches the pattern of cartilage components released from cartilage stimulated in vitro with proinflammatory cytokines.[23,54] Many treatments exist for in vitro cartilage injury suggesting potential benefit. These biomarker observations provide great hope that disease-modifying therapies are within reach for early preclinical OA when it can be diagnosed reliably because there are already many pharmacologic agents with chondroprotective effects in vitro and in vivo joint injury in animal models and emerging in humans.[23,24,55-57]

POTENTIAL BENEFITS TO AN EARLY DIAGNOSIS OF OSTEOARTHRITIS

Annual medical expenditures in the United States attributable to OA are estimated to be as high as $185.5 billion, or 19% of the aggregate medical expenditures for the U.S. adult population.[58,59] It is generally agreed that the prospect for early diagnosis and intervention in OA would improve the likelihood of disease modification and thereby reduce medical costs, morbidity, and disability. In this regard, OA fits the description provided by Machiavelli more than 500 years ago: "In the beginning of the malady it is easy to cure but difficult to detect, but in the course of time, not having been either detected or treated in the beginning, it becomes easy to detect but difficult to cure."[60] A precedent for improved outcomes with early identification and early treatment now exists for rheumatoid arthritis.[61,62] This paradigm should inform the approach to the diagnosis and treatment of patients with OA.

SUMMARY

There is general agreement that early stages of OA would be more amenable to modification, including halting or slowing the disease process to prevent recalcitrant, disabling, and more costly late stages of the disease. Consensus, however, is needed around a new paradigm of OA that conceives of a pathologic continuum beginning with a preclinical stage; such a conception is the norm for other chronic diseases.[63] This would require a reclassification of the disease from a purely radiographic entity to a disease process with preclinical (characterized by serologic abnormalities such as cartilage extracellular matrix component elevations in body fluids), preradiographic, and radiographic stages. Just as not all radiographic OA progresses, it is likely that not all preclinical or preradiographic OA progresses to later stages. To gain this information, more studies are needed to discern and monitor the disease process from its incipient to its end stages. The scenario of acute joint injury, with a known date of onset, provides a potential gateway to understanding the preclinical stages of OA and offers the most promising context in which to elucidate the continuum of pathologic stages of this joint disorder. Ultimately, it will be important to establish the temporal relationship between changes in imaging markers and symptom onset and the molecular events that predate these manifestations of disease to achieve the goal of ultimately preventing and curing OA.

REFERENCES

1. Cibere J, Zhang H, Garnero P, et al. Association of biomarkers with pre-radiographically defined and radiographically defined knee osteoarthritis in a population-based study. *Arthritis Rheum*. 2009;60(5):1372-1380.
2. Roemer FW, Guermazi A, Felson DT, et al. Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. *Ann Rheum Dis*. 2011;70(10):1804-1809.
3. Guermazi A, Niu J, Hayashi D, et al. Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study). *BMJ*. 2012;345:e5339.
4. Moller I, Bong D, Naredo E, et al. Ultrasound in the study and monitoring of osteoarthritis. *Osteoarthritis Cartilage*. 2008;16(suppl 3):S4-S7.
5. Keen HI, Wakefield RJ, Grainger AJ, et al. Can ultrasonography improve on radiographic assessment in osteoarthritis of the hands? A comparison between radiographic and ultrasonographic detected pathology. *Ann Rheum Dis*. 2008;67(8):1116-1120.
6. Poole R, Blake S, Buschmann M, et al. Recommendations for the use of preclinical models in the study and treatment of osteoarthritis. *Osteoarthritis Cartilage*. 2010;18(suppl 3):S10-S16.
7. Luyten F, Bierma-Zeinstra S, Dell'Accio F, et al. Towards classification criteria for early osteoarthritis of the knee. *Semin Arthritis Rheum*. 2017.
8. Lohmander LS, Englund PM, Dahl LL, et al. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. *Am J Sports Med*. 2007;35(10):1756-1769.
9. Spahn G, Schiltenwolf M, Hartmann B, et al. The time-related risk for knee osteoarthritis after ACL injury. Results from a systematic review. *Orthopade*. 2016;45(1):81-90.
10. Russell C, Pedoia V, Amano K, et al. Baseline cartilage quality is associated with voxel-based T1rho and T2 following ACL reconstruction: a multicenter pilot study. *J Orthop Res*. 2017;35(3):688-698.
11. Lohmander LS, Dahlberg L, Ryd L, et al. Increased levels of proteoglycan fragments in knee joint fluid after injury. *Arthritis Rheum*. 1989;32(11):1434-1442.
12. Lohmander LS. The release of aggrecan fragments into synovial fluid after joint injury and in osteoarthritis. *J Rheumatol Suppl*. 1995;43(Feb):75-77.
13. Lohmander LS, Hoerrner LA, Dahlberg L, et al. Stromelysin, tissue inhibitor of metalloproteinases and proteoglycan fragments in human knee joint fluid after injury. *J Rheumatol*. 1993;20(8):1362-1368.
14. Lohmander LS, Hoerrner LA, Lark MW. Metalloproteinases, tissue inhibitor, and proteoglycan fragments in knee synovial fluid in human osteoarthritis. *Arthritis Rheum*. 1993;36(2):181-189.
15. Lohmander LS, Neame PJ, Sandy JD. The structure of aggrecan fragments in human synovial fluid. Evidence that aggrecanase mediates cartilage degradation in inflammatory joint disease, joint injury, and osteoarthritis. *Arthritis Rheum*. 1993;36(9):1214-1222.
16. Lohmander LS, Roos H, Dahlberg L, et al. Temporal patterns of stromelysin-1, tissue inhibitor, and proteoglycan fragments in human knee joint fluid after injury to the cruciate ligament or meniscus. *J Orthop Res*. 1994;12(1):21-28.
17. Larsson S, Lohmander LS. Struglics A. Synovial fluid level of aggrecan ARGS fragments is a more sensitive marker of joint disease than glycosaminoglycan or aggrecan levels: a cross-sectional study. *Arthritis Res Ther*. 2009;11(3):R92.
18. Struglics A, Hansson M, Lohmander LS. Human aggrecanase generated synovial fluid fragment levels are elevated directly after knee injuries due to proteolysis both in the inter globular and chondroitin sulfate domains. *Osteoarthritis Cartilage*. 2011;19(8):1047-1057.
19. Chockalingam PS, Glasson SS, Lohmander LS. Tenascin-C levels in synovial fluid are elevated after injury to the human and canine joint and correlate with markers of inflammation and matrix degradation. *Osteoarthritis Cartilage*. 2013;21(2):339-345.
20. Zhang L, Yang M, Marks P, et al. Serum non-coding RNAs as biomarkers for osteoarthritis progression after ACL injury. *Osteoarthritis Cartilage*. 2012;20(12):1631-1637.
21. Lohmander LS, Atley LM, Pietka TA, et al. The release of crosslinked peptides from type II collagen into human synovial fluid is increased soon after joint injury and in osteoarthritis. *Arthritis Rheum*. 2003;48(11):3130-3139.
22. Aurich M, Squires GR, Reiner A, et al. Differential matrix degradation and turnover in early cartilage lesions of human knee and ankle joints. *Arthritis Rheum*. 2005;52(1):112-119.
23. Catterall JB, Stabler TV, Flannery CR, et al. Changes in serum and synovial fluid biomarkers after acute injury (NCT00332254). *Arthritis Res Ther*. 2010;12(6):R229.
24. Lattermann C, Proffitt M, Huston L, et al. A multicenter study of early anti-inflammatory treatment in patients with acute ACL tear. *Am J Sports Med*. 2017;45(2):325-333.
25. Struglics A, Larsson S, Kumahashi N, et al. Changes in Cytokines and Aggrecan ARGS Neoepitope in Synovial Fluid and Serum and in C-Terminal Crosslinking Telopeptide of Type II Collagen and N-Terminal Crosslinking Telopeptide of Type I Collagen in Urine Over Five Years After Anterior Cruciate Ligament Rupture: An Exploratory Analysis in the Knee Anterior Cruciate Ligament, Nonsurgical Versus Surgical Treatment Trial. *Arthritis Rheumatol*. 2015;67(7):1816-1825.
26. Orlowsky EW, Kraus VB. The role of innate immunity in osteoarthritis: when our first line of defense goes on the offensive. *J Rheumatol*. 2015;42(3):363-371.
27. Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. *Ther Adv Musculoskelet Dis*. 2013;5(2):77-94.
28. Atukorala I, Kwoh CK, Guermazi A, et al. Synovitis in knee osteoarthritis: a precursor of disease? *Ann Rheum Dis*. 2016;75(2):390-395.
29. Blumenfeld O, Williams FM, Hart DJ, et al. Association between cartilage and bone biomarkers and incidence of radiographic knee osteoarthritis (RKOA) in UK females: a prospective study. *Osteoarthritis Cartilage*. 2013;21(7):923-929.
30. Golightly Y, Marshall S, Kraus V, et al. Serum cartilage oligomeric matrix protein, hyaluronan, high-sensitivity C-reactive protein, and keratan sulfate as predictors of incident radiographic knee osteoarthritis: differences by chronic knee symptoms. *Osteoarthritis Cartilage*. 2010;18(suppl 2):S62-S63.
31. Chaganti RK, Kelman A, Lui L, et al. Change in serum measurements of cartilage oligomeric matrix protein and association with the development and worsening of radiographic hip osteoarthritis. *Osteoarthritis Cartilage*. 2008;16(5):566-571.
32. Kelman A, Lui L, Yao W, et al. Association of higher levels of serum cartilage oligomeric matrix protein and N-telopeptide crosslinks with the development of radiographic hip osteoarthritis in elderly women. *Arthritis Rheum*. 2006;54(1):236-243.
33. Dragomir AD, Kraus VB, Renner JB, et al. Serum cartilage oligomeric matrix protein and clinical signs and symptoms of potential pre-radiographic hip and knee pathology. *Osteoarthritis Cartilage*. 2002;10(9):687-691.
34. Ling SM, Patel DD, Garnero P, et al. Serum protein signatures detect early radiographic osteoarthritis. *Osteoarthritis Cartilage*. 2009;17(1):43-48.
35. Luyten F, Bierma-Zeinstra S, Dell'Accio F, et al. Towards classification criteria for early osteoarthritis of the knee. *Annals Rheum Dis*. 2017.
36. van Valburg AA, Wenting MJ, Beekman B, et al. Degenerated human articular cartilage at autopsy represents preclinical osteoarthritic cartilage: comparison with clinically defined osteoarthritic cartilage. *J Rheumatol*. 1997;24(2):358-364.
37. Thorstensson CA, Andersson ML, Jonsson H, et al. Natural course of knee osteoarthritis in middle-aged subjects with knee pain: 12-year follow-up using clinical and radiographic criteria. *Ann Rheum Dis*. 2009;68(12):1890-1893.
38. Peat G, Thomas E, Duncan R, et al. Is a "false-positive" clinical diagnosis of knee osteoarthritis just the early diagnosis of pre-radiographic disease? *Arthritis Care Res (Hoboken)*. 2010;62(10):1502-1506.
39. Zengini E, Finan C, Wilkinson JM. The Genetic Epidemiological Landscape of Hip and Knee Osteoarthritis: Where Are We Now and Where Are We Going? *J Rheumatol*. 2016;43(2):260-266.
40. Lories RJ, Luyten FP. The bone-cartilage unit in osteoarthritis. *Nat Rev Rheumatol*. 2011;7(1):43-49.
41. Manno RL, Bingham CO 3rd, Paternotte S, et al. OARSI-OMERACT initiative: defining thresholds for symptomatic severity and structural changes in disease modifying osteoarthritis drug (DMOAD) clinical trials. *Osteoarthritis Cartilage*. 2012;20(2):93-101.
42. Muehleman C, Margulis A, Bae WC, et al. Relationship between knee and ankle degeneration in a population of organ donors. *BMC Med*. 2010;8:48.
43. Catterall JB, Hsueh MF, Stabler TV, et al. Protein modification by deamidation indicates variations in joint extracellular matrix turnover. *J Biol Chem*. 2012;287(7):4640-4651.
44. Catterall JB, Zura RD, Bolognesi MP, et al. Aspartic acid racemization reveals a high turnover state in knee compared with hip osteoarthritic cartilage. *Osteoarthritis Cartilage*. 2016;24(2):374-381.
45. Zhang R, Yao J, Xu P, et al. A comprehensive meta-analysis of association between genetic variants of GDF5 and osteoarthritis of the knee, hip and hand. *Inflamm Res*. 2015;64(6):405-414.
46. Devereux RB, Alderman MH. Role of preclinical cardiovascular disease in the evolution from risk factor exposure to development of morbid events. *Circulation*. 1993;88(4 Pt 1):1444-1455.
47. Sharif M, Kirwan JR, Elson CJ, et al. Suggestion of nonlinear or phasic progression of knee osteoarthritis based on measurements of serum cartilage oligomeric matrix protein levels over five years. *Arthritis Rheum*. 2004;50(8):2479-2488.
48. Onnerfjord P, Khabut A, Reinholt FP, et al. Quantitative proteomic analysis of eight cartilaginous tissues reveals characteristic differences as well as similarities between subgroups. *J Biol Chem*. 2012;287(23):18913-18924.
49. Vincent TL. Targeting mechanotransduction pathways in osteoarthritis: a focus on the pericellular matrix. *Curr Opin Pharmacol*. 2013;13(3):449-454.
50. Scanzello CR, Plaas A, Crow MK. Innate immune system activation in osteoarthritis: is osteoarthritis a chronic wound? *Curr Opin Rheumatol*. 2008;20(5):565-572.
51. Riyazi N, Slagboom E, de Craen AJ, et al. Association of the risk of osteoarthritis with high innate production of interleukin-1beta and low innate production of interleukin-10 ex vivo, upon lipopolysaccharide stimulation. *Arthritis Rheum*. 2005;52(5):1443-1450.
52. Goekoop RJ, Kloppenburg M, Kroon HM, et al. Low innate production of interleukin-1beta and interleukin-6 is associated with the absence of osteoarthritis in old age. *Osteoarthritis Cartilage*. 2010;18(7):942-947.
53. Luyten FP, Lories RJ, Verschueren P, et al. Contemporary concepts of inflammation, damage and repair in rheumatic diseases. *Best Pract Res Clin Rheumatol*. 2006;20(5):829-848.
54. Kraus V. Biomarkers and Osteoarthritis. In: Ginsburg GS, Willard H, eds. *Genomic and Personalized Medicine*. 2nd ed. Academic Press; 2013:983-989.
55. Lotz MK, Kraus VB. New developments in osteoarthritis. Posttraumatic osteoarthritis: pathogenesis and pharmacological treatment options. *Arthritis Res Ther*. 2010;12(3):211.
56. Olson SA, Furman BD, Kraus VB, et al. Therapeutic opportunities to prevent post-traumatic arthritis: lessons from the natural history of arthritis after articular fracture. *J Orthop Res*. 2015;33(9):1266-1277.
57. Kraus VB, Birmingham J, Stabler TV, et al. Effects of intraarticular IL1-Ra for acute anterior cruciate ligament knee injury: a randomized controlled pilot trial (NCT00332254). *Osteoarthritis Cartilage*. 2012;20(4):271-278.
58. Kotlarz H, Gunnarsson CL, Fang H, et al. Insurer and out-of-pocket costs of osteoarthritis in the US: evidence from national survey data. *Arthritis Rheum*. 2009;60(12):3546-3553.
59. Murphy LB, Helmick CG, Cisternas MG, et al. Estimating medical costs attributable to osteoarthritis in the US population: comment on the article by Kotlarz et al.

Arthritis Rheum. 2010;62(8):2566-2567, author reply 2567-2568.
60. Machiavelli N The Prince: Concerning Mixed Principalities: Constitution Society; 1505. Available from: http://www.constitution.org/mac/prince00.htm.
61. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2010;69(9):1580-1588.
62. Dale J, Porter D. Pharmacotherapy: concepts of pathogenesis and emerging treatments. Optimising the strategy of care in early rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2010;24(4):443-455.
63. Kraus V. Waiting for action on the osteoarthritis front. *Curr Drug Targets*. 2010;11(4):1-2.
64. Kraus VB, Blanco FJ, Englund M, et al. Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. *Osteoarthritis Cartilage*. 2015;23(8):1233-1241.
65. Emrani PS, Katz JN, Kessler CL, et al. Joint space narrowing and Kellgren-Lawrence progression in knee osteoarthritis: an analytic literature synthesis. *Osteoarthritis Cartilage*. 2008;16(8):873-882.